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## The D-Dimer test in combination with a decision rule for ruling out deep vein thrombosis in primary care:

diagnostic technology update

### Clinical Question

In patients presenting in primary care with suspected deep vein thrombosis (DVT), does a point-of-care D-dimer assay combined with a decision rule accurately rule out DVT, and is this strategy cost effective?

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### ADVANTAGES OVER EXISTING TECHNOLOGY

Usual practice is to refer all patients suspected of having deep vein thrombosis (DVT) for diagnostic testing (ultrasonography). However, 80% to 90% of referred patients do not have DVT.<sup>1</sup> Therefore, being able to safely exclude DVT at initial presentation would reduce the number of referrals.

### DETAILS OF TECHNOLOGY

D-dimer is a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis, detected using a monoclonal antibody-based method. Several point-of-care (POC) D-dimer tests are available and their diagnostic accuracy and utility have recently been evaluated and reviewed.<sup>2,3</sup> D-dimer levels can be raised in many conditions (for example, cellulitis), therefore decision rules have been developed to aid rule-out of DVT in conjunction with D-dimer testing. Two decision rules for ruling out DVT are available, one of which was specifically developed for primary care (Table 1).<sup>4</sup> Neither of these applies to pregnant women.

### IMPORTANCE

Each year more than 140 000 patients present in UK primary care with signs and symptoms suggestive of leg DVT.<sup>5</sup>

### PREVIOUS RESEARCH

#### Accuracy compared to existing technology

A 2009 meta-analysis reviewed the diagnostic accuracy of two qualitative and two quantitative POC D-dimer tests. The sensitivity ranged from 85% to 96% and overall specificity from 48% to 74%, with the quantitative tests performing the best.<sup>3</sup> A study of 577 primary care patients with suspected DVT assessed the diagnostic accuracy and user-friendliness of four quantitative POC tests and one qualitative test using ultrasonography as the reference test.<sup>2</sup> All D-dimer tests showed high

sensitivity (91–99%) and negative predictive values above 98%. Specificities ranged between 39% and 64%. Of the quantitative tests, the Cardiac Reader® (Roche Diagnostics) and Triage® (Biosite) tests were quicker to perform (approximately 15 minutes), use whole blood (rather than serum), and simpler calibration. The Clearview® Simplify (Inverness Medical) test was also portable, did not require calibration, and used fingerstick samples, but a quarter of users found interpreting the colour change of the test 'moderately difficult'.

A 2006 systematic review of clinical prediction rules with or without D-dimer concluded that patients with a low clinical probability have a prevalence of DVT <5%.<sup>6</sup> The Wells rule accurately categorised patients as having low, moderate, or high clinical probability. In low-probability patients with a negative D-dimer, the diagnosis of DVT could be reliably excluded without ultrasound. It is worth noting the prevalence of thrombosis was 2.9% among patients in primary care with a low probability and a normal D-dimer.<sup>7</sup>

Due to this uncertainty a decision rule specifically for the primary care setting (Table 1) that includes clinical items and the D-dimer assay result has been developed and validated.<sup>1,8,9</sup> Using this rule, patients in the category of low probability based on the new rule had a 0.7% prevalence of thrombosis.<sup>8</sup>

A trial of 1028 patients with suspected DVT using the rule and POC D-dimer test identified 49% of patients at low enough risk to withhold imaging tests (score of ≤3). In the following 3 months, 1.4% of these low-risk patients went on to have venous thromboembolism.<sup>1</sup> Patients who had a score of ≥4 were referred for ultrasonography, of whom 25% had DVT, and of those who had a normal ultrasonogram, 1.1% developed venous thromboembolism during 3-months follow-up. For patients with suspected DVT, the clinical decision rule

**Table 1. Wells Rule and the Primary Care Rule Scoring to rule out deep vein thrombosis (DVT)<sup>4</sup>**

Variables	Wells Rule	Primary Care Rule
Male sex	–	1
Oral contraceptive use	–	1
Presence of active malignancy (within last 6 months)	1	1
Immobilisation paresis/plaster lower extremities	1	–
Major surgery (last 3 months)	1	1
Absence of leg trauma	–	1
Localised tenderness of deep venous system	1	–
Dilated collateral veins (not varicose)	1	1
Swelling, whole leg	1	–
Calf swelling ≥3 cm	1	2
Pitting oedema confined to symptomatic leg	1	–
Previously documented DVT	1	–
Alternative diagnosis at least as likely as DVT	–2	–
Positive D-dimer result	–	6
Cut-off scores for considering DVT as absent	≤1	≤3

together with a POC D-dimer test reduced referral by ~50%, with a low risk of subsequent venous thromboembolic events.

#### Impact compared to existing technology

A study of data from 1086 patients with suspected DVT compared the diagnostic performance of the Wells score and the primary care rule to safely rule out DVT.<sup>4</sup> A POC D-dimer assay was used for all cases and scores for both decision rules were calculated prior to leg ultrasonography, 447 patients (45%) would not need referral for further testing using the Wells rule plus D-dimer, compared with 495 patients (49%) when using the primary care rule plus D-dimer. A venous thromboembolic event occurred during follow-up in seven patients with a low score and negative D-dimer finding, both with the Wells rule (1.6%); and the primary care rule (1.4%); comparable to rates with ultrasonography only.<sup>11</sup> DVT could safely be ruled out using either decision rule in combination with a POC D-dimer test, reducing the number of unnecessary referrals by approximately 50%. Adjusting the relative scoring of the predictors in the primary care rule or adding new predictors found that neither strategy improved the safety or efficiency of the score, concluding that the original score could be safely used to exclude DVT in primary care.<sup>10</sup>

#### Cost-effectiveness and economic impact

One Dutch study examined the cost-effectiveness of a clinical decision rule and a POC D-Dimer assay to exclude DVT in primary care<sup>12</sup> and found that this strategy was marginally cost-saving (€138 [95% confidence interval = 186 to 115]), but also resulted in a quality-adjusted life year (QALY) loss, –0.0025, compared to a strategy where

all patients were referred to a hospital emergency department and diagnosis was based on a decision rule using a lab-based D-Dimer test. The resulting incremental cost-effectiveness ratio of €55 753 is above the Dutch cost-effectiveness threshold of €40 000.

A recent HTA cost-effectiveness analysis developed a decision analytic model to evaluate 18 different strategies for managing patients presenting as outpatients with suspected DVT, without known comorbidity.<sup>13</sup> For thresholds of willingness to pay between £10 000 to £20 000 per QALY the optimal strategy involved discharging patients with a low or intermediate Wells score and negative D-dimer, ultrasound for those with a high score or positive D-dimer, and repeat scanning for those with positive D-dimer and a high Wells score, but negative initial scan. For thresholds of £30 000 or more a similar strategy, but involving repeat ultrasound for all those with a negative initial scan, was optimal. A further study confirmed that combining clinical probability and D-dimer with a single ultrasound is probably the most cost-effective option.<sup>14</sup> The evidence points to the potential of D-dimer combined with clinical decision rules to be cost-effective for patients presenting in primary care with suspected DVT, although there is a need to evaluate this in a UK setting.

#### Relevant guidelines

The NICE draft guidance on the diagnosis and treatment of venous thromboembolic diseases was published on 26 October 2011 and is under consultation. Regarding diagnosis, the draft recommendations cover the 'use of clinical diagnostic scores such as the Wells Score, diagnostic tests for DVT and PE, including ultrasound and D-dimer testing'. Publication is expected in June 2012. (<http://guidance.nice.org.uk/CG/Wave21/5>).

#### Methodology

Standardised methodology was applied in writing this report, using prioritisation criteria, and a comprehensive, standardised search strategy, and critical appraisal. Full details of these are available from [www.madox.org](http://www.madox.org).

#### What this technology adds

Use of D-dimer in conjunction with a clinical prediction rule can rule out lower leg DVT in about half of patients presenting with suspected DVT in primary care. The potential utility in low-prevalence settings, such as primary care, and the cost effectiveness compared to current strategy of referral of all for ultrasound scan currently warrants further evaluation.

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